PROGRESS

OF

MEDICAL SCIENCE.

THERAPEUTICS.

UNDER THE CHARGE OF

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Recent Hypnotics and Analgesics.

As the result of the combined work of the chemist, the pharmacologist, and the therapeutist, there have of late years been given to the profession several new and active remedies. The classes of drugs included under the hypnotics and analgesics have been largely increased, though the value of many of these novelties is still undecided.

Prof. Leech, in a discussion before the Section of Pharmacology and Therapeutics of the British Medical Association, at the meeting held last August, has made an interesting contribution to this subject, and has outlined in a most excellent manner the fields of usefulness of these remedies. His paper is limited, for the most part, to a consideration of the hypnotics connected with the fatty series. In this class, however, are contained all but three of the newer sleep-producing agents, and of these, two, hyoscine and tannate of cannabin, are only old friends with new faces, whilst the third, boldin, or boldo-glucin, has neither been thoroughly investigated nor practically employed.

The following hypnotics have been brought into use in the past seven years: urethan, acetal, methylal, sulphonal, amylhydrate, hypnone, chloralurethan, and chloralamide. The fact that hypnotics have been sought for, and so largely found, amongst combinations connected with the fatty series, is well worthy of note.

The alcoholic radicals, or alkyls, of which methyl and ethyl are familiar examples, tend to give the compounds into which they enter a power of depressing the functions of the higher cerebral centres, and of producing either sleep or that complete insensibility to external impressions known as general anæsthesia; by their further action, the motor and reflex centres are weakened, and eventually the vaso-motor and respiratory centres and the cardiac ganglia lose their power, the nervous centres being affected in the inverse order of their development.

Very little is known as to the laws which govern the appearance of this influence in the various classes of combinations into which the alcoholic radicals enter, but it is possessed by so many of these combinations that pharmacologists have been led to search among them for those which most effectively depress the higher nervous centres without exerting a deleterious influence in other ways, and this search has led to the large addition to our sleep-producing agents shown in the list.

The halogen elements, chlorine, bromine, and iodine, have, too, a tendency to depress the functions of the higher nervous centres, but they likewise tend, more than the alkyls, to depress the functions of the lower centres which preside over respiration and circulation, and they influence the heart more markedly, weakening its action; the combination of an alkyl with chlorine, or the replacement of one or more of the molecules of hydrogen in an alkyl compound by chlorine, will in many cases augment its influence on the nervous system, but at the same time it increases its depressing effects on the circulation and respiration. By combining chloral with other groups, it has been sought in some degree to minimize these possible evils, and the last two substances in the list have been introduced with this view.

Apart from chemical structure, the physical properties of compounds influence their physiological effects; hence it is that some of the combinations into which alcoholic radicals enter are anæsthetic, some hypnotic; anæsthetics being found amongst those substances which are volatile and quickly eliminated, soporifics amongst those which have a heavy molecule, and are either liquid or soluble, so that they may be given by the mouth, and, being absorbed into the blood, may continue to act.

Of the hypnotics introduced in the past ten years, two, acetal and hypnone, have given but little promise of utility, and we have not sufficient data concerning the action of chloralurethan and chloralamide to discuss their relative merits as compared with other hypnotics.

The other newer hypnotics, urethran, methylal, amylhydrate, sulphonal, and paraldehyde, are compared with chloral and the older hypnotics; the advantages and disadvantages of each are pointed out, and the special sphere where each is indicated is suggested.

Like chloral, they possess little, if any, analgesic action; all may at times relieve pain by causing sleep, and rarely they may seem to remove pain, but none of them possesses that wonderful power of preventing pain which opium has.

It is difficult to estimate the relative hypnotic power of drugs, but the order of potency seems to be as follows: 1, sulphonal; 2, amylhydrate; 3, paraldehyde; 4, urethan; 5, methylal; none of these drugs equals chloral in the certainty of its effects. It seems probable that a dose of sulphonal has, as a rule, about the same soporific action as three-fourths of its weight of chloral; and von Mering is of opinion that half a drachm of amylhydrate has the same power as fifteen grains of chloral, or forty-five minims of paraldehyde.

The time in which sleep is brought on will vary much, according to the condition of the stomach at the time of administration; but it depends, too, on the readiness with which they can be absorbed. Urethan, being soluble and non-irritating, is most rapid in its action; a tendency to sleep is often noticed a few minutes after administration. Paraldehyde and amylhydrate are also rapid in their effects, but sulphonal, more than chloral or any other drug, is slow in producing its effects, and two or three hours not infrequently elapse before they are apparent, though at times sleep follows in from one-half to three-quarters of an hour.

The duration of the action of these drugs depends partly on the potency of their cerebral influence, partly on the rapidity of excretion. On the latter account, the hypnotic effects of urethan most quickly pass away; and if the tendency to sleep, soon after its exhibition, be counteracted, its influence is not again observed. Methylal, too, is very quickly eliminated. The other new hypnotics, when given in sufficient doses, seem to produce, like chloral, a sleep of five to seven hours.

After a dose of chloral, a patient is occasionally sleepy during the following morning, and the influence of the drug is sometimes noted on the second night after its administration: this prolonged deferred action is more marked and frequent after sulphonal than after chloral or any other hypnotic; indeed, it is one of the chief objections to the use of sulphonal, and it cannot always be prevented by giving the drug some hours before bedtime. In the weaker hypnotics this deferred action is rarely seen. As regards the possible dangers of these hypnotics: of chloral, a larger dose than twenty grains is capable of producing a fatal result; sulphonal, even in huge doses, has never produced death, though thirty grains caused cyanosis and a semicomatose condition in a patient suffering from arterio-sclerosis. Paraldehyde and urethan seem quite devoid of danger; concerning amylhydrate and methylal we know too little to speak with certainty, but there is reason for believing that in very large doses grave evils may be produced by both.

Among the unpleasant effects connected with the nervous system excitement, instead of sleep, has been known to follow the use of chloral; amylhydrate, too, though very rarely, has produced excitement before sleep. After sulphonal patients sometimes pass a restless and excited night, occasionally there are bewilderment and restlessness, rarely delirium. Paraldehyde is practically free from this inconvenience. It may be that the greater popularity of sulphonal makes us better acquainted with its effects; but none of the other hypnotics seems to produce such disturbances of the nervous system as those reported after sulphonal, though amylhydrate occasionally causes headache, giddiness, and a feeling of drunkenness. All the hypnotics probably have some direct action on the spinal cord, but the comparative influence of the newer hypnotics on spinal centres requires further investigation.

It is with regard to the influence on circulation and respiration that the newer hypnotics differ so markedly from the older. Chloral, under some conditions, in not very large doses, may give rise to danger owing to its effect on the circulation; it may tend to weaken the respiration, though not so powerfully as opium, whose evil effects are seen chiefly in its depressing influence on the respiratory function.

The newer hypnotics are, to a large extent, devoid of this influence, and very rarely affect the circulation and respiration unless given in such doses as are not used medicinally. The newer hypnotics containing alcoholic radicals produce very little effect on circulation and respiration, and in these ways are superior to both chloral and opium. In the case of methane this is what might be expected from the chemical constitution of the drug, for in it we have an alkyl compound, into which carbamic acid also enters; now carbamic acid contains the amidogen group NH_2, which tends to stimulate the respiratory centre, and an ethyl compound of carbamic acid is likely to have communicated to it the special influence of the NH_2 group.

Gastric disturbances do not commonly occur after the exhibition of chloral or any of the newer hypnotics. The flushing, blotchy rashes, and purpura which chloral hydrate produces, owing to its influence on the vascular system, and perhaps, too, on the blood, are not usually seen after any of the newer hypnotics.

The effects of habituation on the action of the newer hypnotics has not yet been settled; it is probable that the system does not readily become tolerant of them, and that the dose does not have to be increased. In the case of sulphonal a cumulative action is possible, but the other hypnotics of this class are not cumulative in their action.

Bromide of potassium is often a satisfactory and safe remedy in many forms of insomnia; but, this failing, we are often bound to resort to some other drug. Recourse to chloral hydrate is a possible cause of great evil; it is seductive, and many have received great injury from it. It seems to be well proved that the system does not get so habituated to chloral that large doses can be taken without danger, and there seems to be good reason for believing that fatal consequences at times arise from a dose which has several times previously been taken with impunity. We ought never at once to order chloral for simple sleeplessness, but should first order one of the newer hypnotics. In slight cases urethan in doses of from 20 to 30 grains, is often very successful. It is not disagreeable, especially when given in a sweetened, slightly flavored mixture; and of all the hypnotics it is the least likely to give rise to dizziness, headache, or other discomfort. It should be given immediately before the patient settles down to sleep, for it is quickly absorbed, and the slightest disturbance may prevent its good influence. Though the effect of the drug is of short duration, the sleep induced is continued naturally. If necessary, the dose may be increased up to two drachms; a larger dose than this at times causes dizziness, if it does not produce sleep.

The tastelessness of sulphonal has rendered it a favorite remedy in simple sleeplessless. Doses of from 10 to 15 grains often fail, and it is necessary to raise the dose to 20 or 30 grains; larger doses are sometimes recommended, but, from doses above 20 grains, troubles affecting the nervous system are sufficiently common to render some warning to the patient with regard to their possible occurrence desirable. It should be administered, finely powdered, in soup or warm milk, some hours before bedtime.

Paraldehyde is a nauseous remedy, and no one can take it secretly, as the breath always indicates the nature of the drug swallowed. Amylhydrate should be administered in plenty of water, as eight parts of water are required to dissolve one of it.

Hypnotics may sometimes be used in combination when they fail singly; chloral and urethan are often of signal benefit. When sleeplessness is due to pain no other drug approaches opium in value; after opium, though at a long interval, comes chloral, and below chloral in efficacy come the other hypnotics, urethan being the weakest of all.

In cardiac affections accompanied by sleeplessness opium stands out prominently as the best soporific, especially when given in the form of subcutaneous injections. Chloral hydrate is always to be looked upon with suspicion; the more harmless soporifics should be tried first.

In the sleeplessness attending lung affections opium is, of course, out of the question; chloral should be used after milder remedies have been tried. Amylhydrate seems to have some advantages over the others in these cases.

Where delirium is associated with sleeplessness, as in delirium tremens, the milder hypnotics usually fail unless given in very full doses, and urethan is of little value. The older hypnotics, chloral and bromide of potasium, are more effective remedies. In cases of sleeplessness with delirium hyoscine is often used with much advantage, especially where great mental disturbance is accompanied by considerable excitement of the circulation. In mental diseases chloral in continued doses may give rise to serious evils, and opium is a two-edged sword; bromide of potassium often fails, unless given in quantities to affect seriously the heart; urethan is too feeble; sulphonal, paraldehyde, and amylhydrate, all have their advocates, and in moderate doses seem worthy of trial. As amylhydrate has been known to produce very serious effects when given in excessive doses, and sulphonal, in large amounts, is capable of giving rise to unpleasant nervous phenomena, it appears probable that paraldehyde is the best drug to give when hypnotics have to be administered in full doses and continuously. Dr. Clouston, after long experience, believes that in mental cases paraldehyde is the purest and least harmful hypnotic when insomnia is marked and intractable. He begins with 40 minims or a drachm, and goes up to 2 drachms in ordinary cases, sometimes 3 or 4. Sulphonal, he says, will not compare with it. Other observers praise sulphonal, especially if given in small and repeated doses.—*British Medical Journal*, November 2, 1889.

SOMNAL.

A new hypnotic, which has been named somnal, by some somnol, is described in a Berlin pharmaceutical journal by HERR RADLAUER, who states that, chemically, it is ethylated chloral-urethan. It has a melting-point of 107° F. It is not acted upon by nitrate of silver or by acids, and may be prescribed in half-drachm doses, dissolved in water with a little syrup of some kind. As a rule, such a dose as this acts in about half an hour, and produces six or eight hours' sleep. No unpleasant after-effects have been observed. There appears to be no interference with the digestive, circulatory, or respiratory organs, so that, according to the writer, the new drug has all the advantages of chloral without its disadvantages.—*Lancet*, November 16, 1889.

SACCHARIN AS A MEANS OF ACIDIFYING THE URINE.

While it is usually not difficult to render an acid urine alkaline, our means of rendering an alkaline urine acid are less satisfactory.

When saccharin was first announced, it was mentioned among its properties that it was unaffected by the digestive fluids, and was eliminated unchanged in the urine. Some time later **Dr. Andrew H. Smith** had occasion to manipulate with this substance, and was struck with its strongly acid property; it occurred to him that so decided an acid, of such a stable composition as to resist decomposition in the system, and electing the kidneys as its way of exit from the body, would supply exactly the agent required for acidifying the urine.

The idea was tested on a boy suffering with transverse myelitis, whose urine, which required to be drawn with the catheter, was ammoniacal and very offensive. A few grains of saccharin, administered three times a day, promptly changed the reaction of the urine to acid, and did away completely with the offensive odor; not only so, but the irritation of the bladder became less and the formation of pus was diminished.

Shortly after this, Dr. Smith was in attendance upon a case of subacute meningitis in a child twenty months old. The urine, which dribbled constantly into the diaper, was alkaline, and its odor, though not ammoniacal, was peculiarly sickening. Every effort was made in the way of cleanliness, but the atmosphere about the bed was extremely disagreeable. Small doses of saccharin were prescribed, and immediately removed the fetor, to the great relief of the parents and attendants.

A third case was that of a woman of eighteen who was suffering from acute cystitis. The urine was alkaline and contained a large amount of ropy mucus and pus. An attempt to wash out the bladder was abandoned, on account of the severe tenesmus excited. The contact of the catheter with the wall of the bladder caused hemorrhage. Five grains of saccharin were administered, three times a day; on the following day the urine was neutral, and in four days more it was acid, and contained no mucus and but very little pus. Ten days later the urine was entirely normal, the symptoms had disappeared completely, and the patient was discharged cured.

It is probable that a part of the efficacy of saccharin in these cases is due to its being a powerful antiseptic, in addition to its acid property.—*Medical Record*, November 16, 1889.

SOME OF THE RECENT APPLICATIONS OF MENTHOL.

The most familiar employment of this camphor is as a local application for the relief of pain, and menthol cones are prepared and sold in the shops for this purpose. The relief obtained by such applications is usually but temporary, yet in some of the milder forms of facial neuralgia and so-called rheumatic pains the remedy is of real service. In pruritus, also, the analgesic properties of the drug have been turned to good account. It is employed for this purpose in ointment, spirit, or liniment, in the strength of from one part in twenty to one part in ten. A very good preparation for this purpose is that recommended by Eloy, of a solution of fifteen grains of menthol in one ounce of forty per cent. alcohol.

Still another use for the remedy, as externally applied, is in the treatment of furunculosis, and more especially of furunculosis of the external auditory canal. Here the bactericidal properties of the drug, as well as its analgesic action, come into play. **Dr. Cholewa** has made trial of menthol in these cases, and commends it most highly. He applies it by means of a pledget of cotton moistened with a twenty per cent. solution, and inserted into the canal. The application is said to cause a little smarting at first, but this is soon succeeded by entire relief of pain, and a speedy subsidence of the inflammatory process.

Ringworm of the scalp is said by **Mr. Malcolm Morris** to yield more promptly to applications of menthol than to any of the ordinary remedies employed for this purpose. One part of menthol, four of chloroform, and twelve of olive oil is the formula recommended in such cases. In the treatment of various affections of the upper air-passages, also, good results have been obtained in local applications of menthol in the form of solution, vapor, or spray. Decided improvement has followed its use in cases of laryngeal phthisis.

For nasal and pharyngeal catarrh much benefit is often derived from sprays of menthol dissolved in oil or fluid vaseline, in the strength of from one to twenty or thirty per cent. In hay fever **William Hill**, of London, has found menthol to serve an excellent purpose as a substitute for cocaine. He applies a ten or twenty per cent. solution in olive or almond oil to the sensitive area within the nose by means of a brush or atomizer. In the chronic bronchitis of old age, Nyes speaks favorably of inhalations of menthol, which, he says, not only facilitate and rapidly diminish the expectoration, but also allay the cough and reduce the number of paroxysms. These inhalations have also been used with good effect in whooping-cough. Finally, the same mode of application has proved useful in Jores's hands in relieving asthma. Inhalations of a twenty per cent. solution in olive oil were then tried, with the most satisfactory results—the rattling râles disappeared almost immediately, and the respiration soon became normal.

Menthol has not yet been employed to any extent internally, although it is said to act efficiently when so given in controlling certain painful affections. The dose for internal administration is from fifteen to sixty grains per day.

If the effects obtained should be found to be uniformly produced, we might well be justified in placing menthol among the most valuable of the minor therapeutic agents.—*Medical Record*, November 23, 1889.

ACTION OF THALLIN.

M. **Albert Robin** has made a careful study of the physiological action of thallin, especially in regard to its effects upon the chief constituents of the urine. The tests were made upon healthy men, between sixty-one and sixty-eight years old, and the dose of thallin given was, as a rule, fifteen grains, though at times as much as forty-five grains were administered.

It was found that this drug diminishes the total amount of excretion; the organic constituents are lessened to a greater extent than the inorganic, except that the elimination of phosphoric acid and of compounds of sulphur and potassium is increased. The destruction of tissues rich in sulphur seems to continue after the thallin is discontinued.

From such observations he infers that thallin acts as a poison to the nervous system, the red blood-corpuscles and organic tissues rich in sulphur and phosphorus. Its antipyretic properties are believed not to depend upon any direct antiseptic action, but to be the consequence of a toxic action on the red blood-corpuscles and on the nervous system. Consequently, thallin ought not to be prescribed in fevers, as it is a dangerous antipyretic. In a word, the inference from these experiments is that thallin should not be used—this study of its effects upon nutrition suggests only contra-indications.—*Archives de Physiologie*, October, 1889.

Treatment of Chronic Cystitis.

Prof. v. Mosetig-Moorhof recommends half a drachm of the following emulsion injected into the bladder, after previous cleansing, in a pint of water:

℞.—Iodoform	ʒxiij.
Glycerin	℥x.
Distilled water	℥iiss.
Gum tragacanth	grs. iv.—M.

The injection should be made on every third day. After three or four injections the catarrhal inflammation is much or wholly relieved.—*Therapeutische Monatshefte*, October, 1889.

Nocturnal Incontinence of Urine.

A combination of bromide of potassium and tincture of belladonna is recommended as superior to either of these agents alone. Before retiring, ten grains of the bromide should be taken, and at the same time from ten to twenty drops of the tincture of belladonna.—*Therapeutische Monatshefte*, October, 1889.

Naphthalin and Cataract.

Dr. Kolinski, writing in von Graefe's *Archiv*, vol. xxv. 2, points out that naphthalin, which is coming a good deal into use from the effect it seems to have on the microörganisms existing in the intestines in some cases of diarrhœa, possesses also the property of producing changes in the nutritive power of the blood, thus being liable to set up degeneration of the bloodvessels. As the eye is one of the most highly vascular organs, it is one of the first to show any of the changes induced by interference with the nutritive property of the blood. Naphthalin is said first to cause small extravasations in the choroid and in the ciliary body, then ecchymoses and white patches in the retina, and, finally, cloudiness in the lens and crystals in the vitreous.—*Lancet*, November 16, 1889.

Incompatibility of Antipyrin and Chloral.

M. Blainville, a pharmacist of Paris, was called upon to put up a prescription containing sixty grains of antipyrin and seventy-five grains of chloral in half an ounce of water. An oily precipitate was immediately thrown down which resembled neither chloral nor antipyrin in taste, but recalled somewhat that of coriander-seed.

A mixture of antipyrin and quinine is also incompatible, both substances being at once precipitated from the solution.—*Medical Record*, November 23, 1889.